IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of: PETER KŰFER , *ET AL.*
Application No.: 09/744,625

Confirmation Number: 3114

Group Art Unit: 1642

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Examiner: Misook Yu, Ph.D.

Title: HETEROMINIBODIES

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Pre-Appeal Brief Request for Review

This request is submitted concurrently with a Notice of Appeal in the above-identified patent application. The Notice of Appeal is timely filed in response to the Final Office Action mailed August 2, 2006, and the Advisory Action mailed December 12, 2006.

A petition under 37 C.F.R. § 1.136(a) for a two-month extension of time to respond is submitted herewith. A response to the Final Office Action was filed on September 29, 2006, which is within two months of the date the Final Office Action was mailed. Therefore, the period for reply expires on the mailing date of the Advisory Action, and extensions of time to reply are calculated from that date.

Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. If it is determined that a fee for a three-month extension of time is required, please charge the fee to the above-referenced deposit account. The Commissioner for Patents is also authorized to credit any overpayments to the above-referenced deposit account.

REMARKS

Claims 1-41 are pending in the application. Claims 1, 2, 4, 6, 7, 19-23, and 26 are currently under examination and stand rejected. Claims 3, 5, 8-18, 24, 25, and 27-41 are currently withdrawn from consideration. In the Final Office Action (FOA) mailed August 2, 2006, prior rejections under 35 U.S.C. §§102 and 103 were withdrawn, and new grounds of rejection under 35 U.S.C. §103 were asserted. A Response to Office Action was filed on September 29, 2006, without claim amendments. In the Advisory Action (AA) mailed December 12, 2006, the outstanding claim rejections were maintained. Arguments are presented below to show that the outstanding claim rejections under 36 U.S.C. §103 in the FOA and AA (collectively, "the Office Actions") are improper because no *prima facie* case of obviousness has been made.

Claim 1, the sole independent claim under examination, recites:

> A multifunctional compound, expressed in and secreted by a mammalian host cell as a fully functional heterodimer of two polypeptide chains, wherein one of said polypeptide chains comprises the constant CH1-domain of an immunoglobulin heavy chain and the other polypeptide chain comprises the constant CL-domain of an immunoglobulin light chain, wherein said polypeptide chains of said multifunctional compound further comprise, fused to said constant domains at least two polypeptide functional domains having different receptor or ligand functions, wherein at least one of said functional domains comprises a non-immunoglobulin portion having receptor or ligand function, wherein further at least two of said different functional domains lack an intrinsic affinity for one another and wherein said polypeptide chains are linked via said immunoglobulin constant domains. (Emphasis added)

Claim Rejections over Müller *et al.*, WO 97/01580, and Shu *et al.*

Claims 1, 2, 4, 6, 7, 19-22, and 26 are rejected under 35 U.S.C. §103 over Müller *et al.* (1998, *FEBS Letters* 422:259-264) as evidenced by WO97/01580, in view of Shu *et al.* (1995, *Immunotechnology* 1:231-241). The rejection is improper because: (a) the disclosure of Shu *et al.* is not properly considered; (b) the references, when combined, do not teach all the claim limitations; and (c) no teaching, suggestion, or motivation to modify the references to produce the claimed invention is provided. (WO97/01580 is cited as a supporting document for a claim limitation that is not at issue)

The Shu *et al.* reference is not properly considered as a whole

When applying 35 U.S.C. §103, "[t]he references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination." M.P.E.P. §2141.II; *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). Shu *et al.*, first cited in the FOA, is characterized as allegedly teaching "making and using a non-

immunoglobulin portion having receptor or ligand function (i.e., immunoglobulin-interleukin-2 fusion protein)." (FOA page 6, lines 12-14; AA sixth paragraph).

In fact, considered as a whole, Shu *et al.* discloses designing and expressing a single chain immunoglobulin interleukin-2 fusion protein that is secreted into tissue culture fluid as a homodimer linked by disulfide bonds in the hinge region of the fusion proteins. The fusion protein includes heavy and light chain variable regions derived from a monoclonal antibody, CH2 and CH3 heavy chain constant domains, and interleukin-2 (IL-2), where the light chain region is linked to CH2 through the functional hinge region, and IL-2 is linked to the CH3 domain (*See* Fig. 1). Further, Shu *et al.* discloses that the fusion protein is designed to ensure homodimer formation through disulfide links in the functional hinge region. (Section 3.1, "Design of the fusion protein" in particular, page 235, right column, lines 13-16). When the disclosure of Shu *et al.* is properly considered as a whole, this reference cannot be used to make a *prima facie* case of obviousness for the claimed invention.

Combining Müller *et al.* with Shu *et al.* does not teach or suggest the invention

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP §2143.03; *In re Royka*, 180 USPQ 580 (CCPA 1974). Müller *et al.* discloses a heterodimer formed by a disulfide bond between the CH1 domain of a first monomer and the CL domain of a second monomer. It is admitted in the Office Actions that Müller *et al.* does not disclose a non-immunoglobulin portion having receptor or ligand function. In contrast, Shu *et al.* discloses an immunoglobulin interleukin-2 fusion protein with CH2 and CH3 domains, that forms a homodimer linked by disulfide bonds in the hinge region. Shu *et al.* does not teach or suggest a heterodimer including the fusion protein, let alone forming a heterodimer via constant domains, much less a heterodimer linked via CH1 and CL domains as in the claimed invention. Combining the teachings of Müller *et al.* and Shu *et al.* does not teach or suggest all the claim limitations of Claim 1 (and claims dependent therefrom) and *prima face* obviousness is not established.

No teaching, suggestion, or motivation to modify references is provided.

To establish a case of *prima facie* obviousness, there must be some suggestion or motivation to combine or modify the teachings of the prior art to produce the claimed invention. *See* MPEP §2143.01. As noted above, merely combining the cited references does not produce the claimed invention. If the claim rejections under 35 U.S.C. §103 rely on modifying the references to produce the claimed invention, then the Office Actions fail to provide any such teaching, suggestion, or motivation to modify the references.

No suggestion or motivation to modify the references can be found in the references themselves. The disclosure in Müller *et al.* is limited to "bispecific miniantibodies" and does not teach or even suggest the desirability of a heterodimer comprising a non-immunoglobulin portion having receptor or ligand function. Shu *et al.* does not teach or even suggest using the fusion protein to form a heterodimer, much less a heterodimer linked via constant domains. In fact, Shu *et al.* discloses that the fusion protein was designed to ensure homodimer formation through the hinge region.

The Office Actions do not teach or suggest how Müller *et al.* could be modified in view of Shu *et al.* to produce the claimed invention. Further, the Office Actions fail to explain why an ordinarily skilled artisan would be motivated to make such modifications. Because no teaching, suggestion, or motivation to modify the references to produce the claimed invention is provided, no *prima face* case of obviousness is established.

Claim Rejections under over Müller *et al.*, Shu *et al.*, and Plückthun and Pack

Claims 1, 2, 4, 6, 7, 19-23, and 26 stand rejected under 35 U.S.C. §103(a) over Müller *et al.* in view of Shu *et al.*, and further in view of Plückthun and Pack (1997, *Immunotechnology* 3:83-105), which is cited for disclosing the use of the upper hinge region from human IgG3. Substituting the linkers of Müller *et al.* with the upper hinge region of human IgG3 taught by Plückthun and Pack was allegedly obvious, with success expected "since combination of Muller et al. (Jan. 1998) and Pluckthun and Pack (1997) teach how to make each elements [*sic*] of the claimed invention." (FOA page 8, line 14; AA, final pararagraph)

The rejection of Claims 1, 2, 4, 6, 7, 19-22, and 26 over the cited references is improper because these claims do not recite the upper hinge region of human IgG.

The rejection of Claim 23, which recites the upper hinge region of human IgG, is improper in light of the Examiner's own admission that Müller *et al.* does not disclose a non-immunoglobulin portion having receptor or ligand function (see above), such that the combination of Müller *et al.* and Plückthun and Pack does not teach all the elements of the invention of Claim 23 as asserted. Furthermore, as shown above, the combination of Müller *et al.* in view of Shu *et al.* does not teach or suggest the claimed invention, and Plückthun and Pack does not cure this deficiency. Therefore, the rejection of Claims 1, 2, 4, 6, 7, 19-23, and 26 is improper and should be withdrawn.

CONCLUSION

For at least the reasons provided above, the outstanding claim rejections under 35 U.S.C. §103 are not supported by a *prima facie* case of obviousness. Therefore, the outstanding claim rejections should be withdrawn in order to permit issuance of a Notice of Allowance of Claims 1, 2, 4, 6, 7, 19-23, and 26 currently under examination.

Respectfully submitted,

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